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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/018,770
Filing Date: December 17, 2001
Appellant(s): IKEDA ET AL.

Gunther J. Evanina
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed November 14, 2005, appealing from the Office action mailed March 29, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

JP 9-117279	5-1997
JP 1-304882	8-1989

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 4, 6-8, 10-14 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 9-117279 in view of JP 1-304882.

The claims are directed to a drug composition comprising two ingredients:

(1) the disaccharide sucrose, and

(2) a "lecithin-modified superoxide dismutase."

The "lecithin-modified superoxide dismutase" refers to the enzyme superoxide dismutase which has at least one lecithin moiety covalently bound to the enzyme. This compound is sometimes referred to as "PC-SOD" herein, which refers to lecithin's alternative name, phosphatidylcholine ("PC"), being covalently bound to superoxide dismutase, or "SOD."

JP '279 discloses the preparation of the claimed lecithin-modified SOD (or "PC-SOD"), for therapeutic uses. See English language abstract; see also page 4 of English translation; see also page 18 of English translation, paragraph [0028],

disclosing the use of PC-SOD in freeze-dried, i.e. lyophilized, applications. JP '279 differs from the cited claims in not combining the SOD derivative with a carrier which allows for the storage properties recited in the claims under examination. However, JP '882 clearly discloses that combination of SOD with sucrose results in a stable SOD preparation suitable for frozen storage. See English language abstract; see also "Embodiment 3", at pages 9 and 10 of the English translation.

Thus, the artisan of ordinary skill seeking to store the SOD derivatives of JP '279, recognizing from JP '882 that addition of sucrose would improve the storage stability of the SOD derivatives, clearly would have been motivated by JP '882 to have combined the SOD derivatives of '279 with sucrose to have rendered them stable for storage. A reasonable expectation of success would have been based on the fact that JP '882 discloses that the very same enzyme was rendered storage stable by combination with sucrose. A holding of obviousness is therefore required.

(10) Response to Argument

It is respectfully submitted that appellant's argument does not demonstrate error. Appellant initially argues that JP '882 states that, although human SOD does not suffer from a decrease in activity, undesirable by-products, mostly dimers, can result

from frozen storage of human superoxide dismutase. Thus, argues appellant, sorbitol, mannitol, inositol, sucrose, trehalose and fructose are disclosed by JP '882 as reducing the presence of an undesirable 79 kD dimer by-product when combined with human SOD, without denaturation by-products being detected, whereas when arabinose, glucose and galactose are combined with human SOD, denaturation occurs, despite reduction in the presence of the 79 kD by-product.

Appellant's argument fails to demonstrate non-obviousness of the claims for several reasons. First, only claims 7 and 8 are limited to human PC-SOD. Thus, to the extent that appellant urges that JP '882 discloses that SOD is not subject to loss of activity upon the freezing and thawing of the storage process, this argument is only applicable to claims 7 and 8. Reading JP '882 in its entirety, JP '882 clearly discloses that the purpose of combining disaccharides with SOD, such as the sucrose recited in the claims under examination, was to avoid denaturation which occurs during the process of freeze-drying SOD. See, JP '882, translation, pages 3-5. For example JP '882 discloses that bovine SOD loses up to 25% activity upon freeze-drying. Thus, JP '882 provides motivation for adding a stabilizing agent such as sucrose at least to bovine SOD, so as to prevent denaturation of the enzyme.

Moreover, with respect to claims 7 and 8, JP '882's disclosure, that sucrose is a better preservative for human SOD than arabinose, glucose and galactose, provides motivation for using sucrose as a stabilizer in the freeze-dried storage applications for the PC-SOD disclosed in JP '729, the PC-SOD of JP '729 being the same enzyme as the SOD of JP '882, except for the lecithin moiety attached thereto.

Appellant further argues that there is an absence of any suggestion in the prior art that PC-SOD is susceptible to denaturation, or that dimerization of PC-SOD would be considered undesirable, or that dimers of PC-SOD would be allergenic in the same manner as the dimers of SOD disclosed in JP '882. In support of this argument appellant points to U.S. Pat. 5,762,929, which discloses the use of PC-SOD as an anti-inflammatory agent without "adverse effect such as antigenicity" or allergenic side effects, the PC-SOD being present as a "homodimer." Appellant further urges that because denaturation of SOD cannot occur until the dimer form of SOD is dissociated into its constituent monomers (Brief, page 6, first full paragraph), one of ordinary skill would not have been motivated to have added sucrose to PC-SOD, because JP '882 discloses that sucrose prevents dimerization.

Appellant's construction of JP '882 must fail for several reasons. It is a fact that like PC-SOD, the active form of SOD is a "homodimer" of two subunits of about 16 to 20 kD, depending on measurement technique. Thus, the active form of the underivatized enzyme can range from about 32 to 40 kD, roughly. The undesirable dimers discussed in JP '882 are disclosed as having a molecular weight of 79 kD. Thus, contrary to appellant's argument, the undesirable dimers prevented by JP '882's combination of sucrose with SOD are undesirable dimers of the active form of the enzyme, not the desirable "homodimers" which are the active form of the enzyme.

Moreover, reading JP '882 to teach away from adding sucrose to SOD flies in the face of the direct disclosure of the reference. Clearly, the reference discloses in a number of places that sucrose is a desirable and advantageous additive to SOD. See, e.g., page 5 of JP '882. This is in fact the central point of the disclosure of JP '882. Reading JP '882 as somehow disclosing that sucrose promotes the degradation of the underivatized enzyme is to ignore the basic thrust of the disclosure therein. The artisan of ordinary skill would not construe JP '882 in a manner that would contradict the basic thrust of the disclosure.

As to whether the prior art recognized any sort of susceptibility of PC-SOD to storage degradation problems, it is respectfully submitted that the present facts do not present a situation where appellant is presenting a solution to an undiscovered problem. Appellant's own specification, at page 2, first full paragraph, under the "Background Art" section, states that while the PC-SOD product was known, the prior art had not solved the problems attendant with long term storage and lyophilization of PC-SOD. Thus, appellant's argument that the prior art did not recognize storage problems with PC-SOD appears to be directly contrary to appellant's own disclosure. Moreover, in view of at least the disclosure of JP '882 that frozen storage of bovine SOD produced denaturation, and storage of human SOD produced undesirable by-products, the artisan of ordinary skill would have reasonably expected PC-SOD, a nearly identical molecule with identical enzymatic activity, to have had similar storage problems.

The disclosure of U.S. Pat. 5,762,929 and its argued failure to discuss storage problems with PC-SOD is noted. However, that reference does not discuss anything specific about the long term storage of PC-SOD, nor is there any specific discussion therein about what techniques should be used for storing the enzyme for long periods. Thus, US '929 is not

directly relevant to the issue of whether PC-SOD suffers from problems with long term storage in freeze-dried form.

However, directly contrary to appellant's argument, US '929 does provide credence to the suggestion that the preservatives for SOD disclosed by JP '882 should also be used with PC-SOD. Specifically, US '929 uses mannitol as the excipient with the injectable liquid, and lactose as part of the tablet formulation. See Example 2, at column 11, lines 45-63 of US '929. JP '882 lists both mannitol and lactose alongside the sucrose claimed by appellant by as being among the desirable preserving additives for SOD. Thus, contrary to appellant's argument, US '929 does not teach away from additives desirable for preserving SOD when looking to additives suitable for PC-SOD. Rather US, '929 discloses that the very same additives disclosed by JP '882 as being useful for preserving SOD are suitable for use in combination with PC-SOD. The fact that the same additives used for SOD preservation are used in the preparation of storage-stable PC-SOD preparations demonstrates that one of ordinary skill would have considered prior art discussing the preservation of SOD relevant to the issue of preserving PC-SOD.

Appellant further argues that one of ordinary skill in the art would recognize that PC-SOD is a chemical substance that is

significantly different than SOD, and that it is "well known" that PC-SOD differs from SOD with respect to its distribution in the living body, and affinity to self, and that it is "well known that PC-SOD retains an extremely uniform activity as compared with SOD, so that it is expected to enhance the pharmacological activity of SOD, reduce side effects, and promote absorption." Brief, page 7. Thus, argues appellant "[b]ecause it is well known that PC-SOD is very different[ly] from SOD" (Brief, page 7), one of ordinary skill would not have expected sucrose to have had the same stabilizing effect on PC-SOD as it does on SOD, particularly since the prior art teaches that sucrose shifts the equilibrium toward monomeric SOD, and therefore closer to denaturation.

Appellant's argument does not demonstrate error. With respect to the repeated assertions of what is "well known" about PC-SOD, it is respectfully pointed out that appellant fails to support any of these assertions with any direct evidence. In this regard note specifically that argument by counsel is not a sufficient substitute for actual evidence. See, e.g., MPEP § 2145, subsection "I", and cases cited therein.

Moreover, appellant's assertion, that PC-SOD is "very different" from SOD, is simply not supported by facts. It is a fact that the claims require only that each superoxide dismutase

be substituted by one, or as few as two, lecithin moieties. Thus, the PC-SOD recited in the claims differs from the sucrose-stabilized SOD of JP '882 only in that it contains a single lecithin moiety attached thereto. **The protein portions of PC-SOD and SOD are identical.** Moreover, PC-SOD and SOD have identical catalytic properties.

As pointed out above SOD is a 32,500 to 40,000 dalton protein. The PC-SOD, as recited in appellant's claims, contains a single pendant phosphatidylcholine group of about 800 daltons attached to the much larger protein molecule. The pendant PC group is therefore much smaller than the protein to which it is attached. Thus, based on the fact that the protein portion of the two molecules is identical, and that the single attached PC molecule is a small portion of the total PC-SOD, one of ordinary skill in the art would have expected the physical properties of PC-SOD to have been fairly similar to the physical properties the underivatized SOD.

Even if it were conceded that certain differences between PC-SOD and SOD were "well known," one of ordinary skill would have recognized that attaching PC to SOD modifies the ***biological properties*** of the compound by increasing its therapeutic availability. However, based on the expected commonality of ***physical properties*** between PC-SOD and SOD, reflected as a

function of the common structural properties discussed above, one of ordinary skill seeking to prepare a lyophilized (freeze-dried) form of PC-SOD as suggested by JP '279 (paragraph [0028]) clearly would not have ignored prior art disclosing ingredients advantageous in lyophilized forms of the closely related compound SOD. Rather, the first prior art the artisan of ordinary skill would have consulted when seeking to prepare lyophilized formulations of PC-SOD would in fact have been prior art directed to preparing lyophilized forms of SOD.

Also, as discussed above, appellant's argument about sucrose promoting denaturation of SOD by shifting the equilibrium toward monomeric SOD, or PC-SOD, is simply incorrect. The entire discussion of JP '882 is to the effect that disaccharides, such as the claimed sucrose, enhance the storage stability of SOD. By reading JP '882 to suggest that sucrose encourages denaturation of the enzyme, appellant is ignoring the basic thrust of the reference. The artisan of ordinary skill simply would not do that. With all due respect, it appears that appellant is confusing the active "homodimer" form of SOD with inactive polymerized forms of the naturally dimerized enzyme. See, e.g., U.S. Pat. 4,966,774 (cited on the PTO Form 892 of August 12, 2005), which discloses, at column 1, lines 35-43, that the combination of phosphate, sodium chloride

and sucrose "give[s] a stable SOD composition scarcely suffering from any ***decrease in the activity or denaturation caused by, for example, polymerization*** . . . ." (Emphasis added.)

Appellant further argues that they have "discovered that there is a loss of biological activity of PC-SOD during freeze-drying and/or freeze-thaw cycles due only to degradation of the phosphatidylcholine (PC) moieties." Brief page 8, emphasis in original. With all due respect, this statement fails to find support in the disclosure as filed, or on the record. First, the statement in the Brief is directly contradicted by the statement at page two of the specification, first full paragraph, under the "Background Art" section, which suggests that while the PC-SOD product was known, the prior art had not solved the problems attendant with long term storage and lyophilization of PC-SOD.

Also, there is not one fact currently on record to support the assertion that loss of activity of PC-SOD upon freeze-drying/freeze/thaw is caused solely by degradation of PC moieties. Review of the data presented in the specification simply demonstrates that sucrose stabilizes the enzymatic activity of PC-SOD better than other known stabilizers, and that there are fewer by-products (termed "analogues") produced upon freezing/storing/thawing. Therefore, contrary to appellant's

argument, there is simply no demonstration of a cause/effect relationship between degradation of the PC moieties of PC-SOD and loss of activity. The record does not support the discovery alleged by appellant.

Appellant lastly argues that the obviousness rejection of record is based on improper hindsight and misinterpretation of the art. However, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case JP '279 clearly discloses the desirability of preparing lyophilized forms of PC-SOD. JP '882 clearly discloses that when sucrose is combined with the nearly identical compound, SOD, in lyophilized preparations, the sucrose prevents denaturation of the bovine version of the protein, as well as preventing formation of undesirable side products in the human version of the protein. Thus, the artisan of ordinary skill, recognizing the advantages of combining sucrose with SOD, clearly would have been motivated to have combined sucrose with the nearly identical molecule PC-

SOD, so as to afford the disclosed advantages of the sucrose stabilizing agent. It is therefore respectfully submitted that a holding of *prima facie* obviousness is proper.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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